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(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM FOR ADMINISTERING ACETYLSALICYLIC ACID AND/OR SALICYLIC ACID

(57) Abstract: The invention relates to a transdermal, therapeutic system in the form of a plaster which contains acetylsalicylic acid and/or salicylic acid. Said system has a backing layer, an active ingredient reservoir attached thereto, a membrane which controls the administration of the active ingredient in the absence of other control mechanisms, an adhesive device for fixing the system onto the skin and a protective layer which can be detached before application. The system is characterised in that it contains at least one component from the group of pyrrol derivatives and at least one component from the group of terpenes.

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Transdermal therapeutic system for administering acetylsalicylic acid and/or salicylic acid

The invention relates to a transdermal therapeutic system, which allows the administration of acetylsalicylic acid or salicylic acid or both active ingredients together to the skin. In addition, it relates to a method for the manufacture of said system.

The active ingredient acetylsalicylic acid is widely used as analgesic, antipyretic substance, inflammation inhibitor and thrombocyte aggregation inhibitor. Acetylsalicylic acid affects the prostaglandin metabolism, thus suppressing the formation of mediator substances, which play a key role in pain- and inflammation-related events. This is achieved with the inhibition of cyclooxygenase, an enzyme of the biosynthetic path of prostaglandin. Therefore, the active ingredient acetylsalicylic acid is assigned to the group of so-called COX-2 inhibitors.
Salicylic acid has an anti-inflammatory action as well; in addition, it is used for its antiseptic and coagulation-inhibiting properties.

The oral administration of acetylsalicylic acid or salicylic acid, in particular the long-term use, is associated with the risk of gastrointestinal side effects, such as microhemorrhages. This disadvantage can be avoided by selecting a mode of administration with which the active ingredient can be applied to the organism by bypassing the gastrointestinal tract. Transdermal administration appears to be particularly suitable for this purpose, subject to the condition that an application system is available, which is capable of releasing the active ingredient acetylsalicylic acid or salicylic acid to the skin from a reservoir over a certain period of time at sufficiently high flow rates.

The permeability of acetylsalicylic acid through human skin and hence its fundamental suitability as a component of skin patches containing the active ingredient is generally known (Journal of Pharmaceutical Science 176 (1987), pp. 451–454). However, the flow of active ingredient obtained this way does not meet the established requirements with respect to the chronological start and the extent of intended pharmacological action, e.g., with respect to the earliest possible inactivation of the thrombocyte-cyclooxygenase.

Based on prior art, a large number of substances are indeed known, which are capable of supporting the penetration of active ingredients through the skin ("enhancers"). The theoretical basics for said enhancer action are largely unknown; however, some attempts have been made to explain the action based on various models (Williams A. C. & Barry B. W., "Skin absorption enhancers," Crit. Rev. Ther. Drug Carrier Syst. (US) 1992, 9/3–4, 305–353).

It is therefore the object of the present invention to provide a transdermal form of administration for the active ingredients acetylsalicylic acid and salicylic acid, which allows an adequate flow of active ingredient in vivo and which can be manufactured in a cost-efficient manner using established manufacturing methods.

Surprisingly, the object is solved with the provision of a transdermal therapeutic system (TTS) in the form of a patch pursuant to claim 1. The TTS according to the invention is characterized in that it comprises at least one component from the group of pyrrole derivatives and at least one component from the group of terpenes. The mutual presence of components from both groups leads to an unexpected increase of the transport of active ingredient through the skin in vivo (cf. Tab. 1 and Fig. 1).

From the group of the pyrrole derivatives, 2-pyrrolidone has proven to be particularly active. However, other pyrrole derivatives can be used successfully, where it is also possible to use

two or more compounds from this group.

From the group of terpenes, limonene is particularly suitable; however, natural terpene mixtures for which the main component is limonene, such as, e.g., lemon oil (oleum citri) can also be used. However, other terpenes, individually or combined, can also be used as component of the TTS according to the invention.

To achieve an optimal flow of active ingredient, the use of components from the group of pyrrole derivatives at a concentration ranging from 0.1–15%, preferably from 2 to 10% and the components from the group of terpenes at a concentration ranging from 1–30%, preferably from 10–20%, has proven to be particularly advantageous, where the indicated percentages each refer to the whole mass of the matrix.

The TTS according to the invention preferably comprises a layer-like composition with at least one polymer matrix layer. The latter can at the same time act as active ingredient reservoir. In the individual case it may be preferable if the TTS according to the invention comprises two or more matrix layers. They can consist of different active ingredients or different concentrations of active ingredient. In addition, the individual matrix layers can differ with respect to the enhancer content or other additives.

Moreover, the matrix layer can consist of adhesive material to allow the fixation of the patch on the skin. If the reservoir containing the active ingredient is not adhesive or the adhesion is inadequate, it can be combined with a special adhesive device which ensures the constant contact of the system with the skin. Identical materials as the ones used for the polymer matrix of the active ingredient reservoir can be used for this purpose.

To allow the controlled the release—if not provided for by means of other mechanisms—the reservoir can be equipped with a control membrane used to control the release of the active ingredient to the skin.

The polymer matrix layers of the TTS according to the invention are preferably made of polymers selected from the group comprising polyacrylic acid ester and its copolymers, (meth)acrylate-based polymers, ethylene vinyl acetate copolymers, polyisobutylenes, polyterpenes, cellulose derivatives, rubbers, synthetic rubbers and hot-melt adhesives. Copolymers made of 2-ethylhexyl acrylate, vinyl acetate and acrylic acid with or without crosslink are preferred as acrylate-based polymers. Copolymers based on dimethylamino methacrylate and neutral methacrylic acid esters are preferably used as polymethacrylate. Styrol- and 1,3-diene-based block copolymers, such as linear styrol isoprene block polymers, are preferably used as synthetic rubbers. Alternatively, polymer mixtures can also be used.

In a particularly preferred embodiment of the invention, at least one matrix layer comprises polymer components selected from the group of substituted celluloses, preferably methyl or ethyl celluloses. In another preferred embodiment, it is intended that at least one matrix layer comprises ester of the hydrated colophonium, preferably its methyl or glycerin ester. The mechanical properties of the TTS, such as cohesion and adhesion/tack, can be affected by the selection of the matrix polymers and the other matrix components.

According to the preamble of the main claim, the layer-like composition of the TTS according to the invention additionally comprises an impermeable backing layer as well as a detachable protective layer. Polyesters which are particularly strong and diffusion-proof are especially suitable for the backing layer besides almost any other dermatologically safe synthetics such as polyvinyl chloride, ethylene vinyl acetate, vinyl acetate, polyethylene, polypropylene, cellulose derivatives and many more. In the individual case, the backing layer can comprise an additional

coat, e.g., created by means of vaporization of metals or other diffusion inhibiting additives such as silicium dioxide, aluminum oxide or similar substances known to the person skilled at the art. The same materials used for the backing layer can be used for the detachable protective layer, provided that they have been rendered detachable by means of a suitable surface treatment such as, e.g., siliconization. However, other detachable protective layers such as paper treated with polytetrafluoroethylene, cellophane, polyvinyl chloride or similar materials can be used.

To improve the action of the TTS according to the invention, or to adjust them to different requirements, additional additives or admixtures can be added. Especially softeners and permeation accelerators should be considered in this respect. Furthermore, tackifiers, stabilizers, fillers and carrier substances can be added. The pharmaceutically harmless additives which may be used for this purpose are known to the person skilled at the art.

Compounds from the group of hydrocarbons, alcohols, carbonic acids and their derivatives, ether, ester or amines are preferably used as softeners, where individual softener compounds can be used in combination. A preferred embodiment of the invention provides for a softener content of 0–30%, preferably 5–20%, each with respect to the total mass of the matrix.

Another preferred embodiment is characterized in that the TTS contain a natural or partially synthesized triglyceride or a mixture of said triglycerides at a concentration ranging from 0–30%, preferably from 5–20% with respect to the total mass of the matrix.

An additional increase in the release of the active ingredient is made possible based on the exemplary embodiment described in subclaim 13, which provides that the TTS permeation accelerators from the group of the polyoxyethylene derivatives and non-ionic tensides preferably contain sorbitan fatty acid ester. The concentration of the permeation accelerator(s) ranges

between 0–5%, preferably between 1–3%, with respect to the total mass of the matrix.

Generally, the active ingredient acetylsalicylic acid or salicylic acid is available in dispersed or diluted form or distributed as homogeneously as possible in one or more polymer matrix layers of the TTS according to the invention. According to a special embodiment, the active ingredient can also be provided in a bag-shaped reservoir, filled with a liquid, highly viscous, semi-solid or thixotropic matrix containing the active ingredient. It is especially preferred if the semi-solid or thixotropic active ingredient reservoir comprises a gellant. The back of the bag facing away from the skin must be active ingredient-impermeable and the side facing the skin active ingredient-permeable. Optionally, an active ingredient-permeable membrane can assume the control of the active ingredient release.

To allow the best possible release rate, the highest possible active ingredient concentration is preferably aimed for in the active ingredient-containing layers, where we would like to emphasize that the stability of the system can be negatively impacted if the concentrations are too high. Therefore, active ingredient concentrations ranging from 5–75%, in particular from 15–45% with respect to the total mass of the active ingredient-containing layers are preferable in the TTS according to the invention.

The following examples are intended to explain the invention in detail.
The increased release of acetylsalicylic acid and/or salicylic acid in the TTS according to the invention is illustrated based on the measured values listed in table 1 and the graphical illustration in Fig. 1. They show that a significant increase in the penetration of the human skin was always recorded with the TTS comprising a combination of 2-pyrrolidone and a terpene mixture according to the invention; this is true both when only one active ingredient is used at a time (ASA or SS) or when both active ingredients are combined.

The TTS used for the determination of the human skin penetration were manufactured as follows:
1) First, 2-pyrrolidone and ASA were dispersed in a polyacrylate adhesive, resulting in a suspension which was coated onto a 100 µm PET foil (release liner/protective layer). After drying, said laminate was covered by HDPE foil (intermediate liner), rolled up and stored protected from moisture. Said dried laminate is referred to as laminate layer 1.
2) Oleum citri and a polymethacrylate (Plastoid® B) were processed to create a homogeneous viscous solution and coated onto a 19 µm PET foil (backing layer), resulting in laminate layer 2 (moist).
3) Laminate layer 1 was used to laminate the moist laminate layer 2. The resulting double-layered laminate was rolled up into a wide roll. The latter was cut into narrow rolls which were made into single ASA-TTS.
A corresponding formulation without 2-pyrrolidone was used as a reference example (no. 8271508).

The permeation rates through human skin were determined using Franz diffusion cells.

The results of the permeation assays are summarized in table 1. The lines labeled "SS," "ASA" and "ASA sum" refer to the release values obtained with TTS which either contained salicylic acid or acetylsalicylic acid or acetylsalicylic acid combined with salicylic acid.
The values in the columns of the table reflect the amount of released active ingredient (in µg) per unit of area (cm^2).

Figure 1 shows a graphic illustration of the data contained in table 1.

Assay	Release of ASA, SS and sum (ASA + SS) [µg/cm²]						Composition	
		0	4 h	8 h	24 h	48 h	Component	%
5189/1	ASA sum	0	22	97	405	686	ASA 63 µm [sic]	19.05
							Durotak 381-2052	56.35
	ASA	0	13	50	156	233	Plastoid B	8.25
							Oleum citri	12.38
	SS	0	7	36	190	347	2-pyrrolidone	3.97
8271508	ASA sum	0	2	21	194	430	ASA 63 µm [sic]	19.05
							Durotak 381-2052	60.32
	ASA	0	1	7	52.2	102	Oleum citri	12.38
							Plastoid B	8.25
	SS	0	1	10	109	252		

Table 1

Claims

1. Acetylsalicylic acid and/or salicylic acid-containing transdermal therapeutic system in patch form, comprising a backing layer, an active ingredient reservoir associated with it, a membrane controlling the active ingredient release in case no other control mechanism is provided, an adhesive device to fix the system on the skin and a protective layer which is detached prior to the application, characterized in that it comprises at least one component from the group of pyrrole derivatives and at least one component from the group of terpenes.

2. Transdermal therapeutic system according to claim 1, characterized in that at least 2-pyrrolidone is selected as a component from the group of pyrrole derivatives.

3. Transdermal therapeutic system according to claim 1 or claim 2, characterized in that at least limonene is selected as a component from the group of the terpenes.

4. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that it comprises a natural terpene mixture with limonene as its main component.

5. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the components from the group of pyrrole derivatives are used at a concentration ranging from 0.1–15%, preferably from 2 to 10%, and the components from the group of terpenes at a concentration ranging from 1–30%, preferably from 10–20%, each with respect to the total mass of the matrix.

6. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that it comprises a layer-like structure with at least one polymer matrix layer.

7. Transdermal therapeutic system according to claim 6, characterized in that at least one matrix layer comprises polymer components selected from the group comprising polyacrylic acid ester and its copolymers, (meth)acrylate-based polymers, polyacrylates, polyisobutylenes, polyterpenes, ethylene vinyl acetate copolymers, cellulose derivatives, rubbers, synthetic rubbers and hot-melt adhesives.

8. Transdermal therapeutic system according to claim 6 or claim 7, characterized in that at least one matrix layer comprises polymer components selected from the group of substituted celluloses, preferably methyl or ethyl celluloses.

9. Transdermal therapeutic system according to one or more of claims 6 to 8, characterized in that at least one matrix layer comprises esters of the hydrated colophonium, preferably its methyl or glycerin ester.

10. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that it comprises one or more softeners, selected from the group comprising hydrocarbons, alcohols, carbonic acids and their derivatives, ether, ester or amines.

11. Transdermal therapeutic system according to claim 10, characterized in that it comprises softeners at a concentration ranging from 0–30%, preferably from 5–20% with respect to the total mass of the matrix.

12. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that it comprises a natural or partially synthetic triglyceride or a mixture of said triglycerides at a concentration ranging from 0–30%, preferably ranging from 5–20% with respect to the total mass of the matrix.

13. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that it comprises at least one permeation accelerator selected from the group comprising polyoxyethylene derivatives and non-ionic tensides, preferably sorbitan fatty acid ester, where the concentration of the permeation accelerator(s) ranges between 0–5%, preferably between 1–3% with respect to the total mass of the matrix.

14. Transdermal therapeutic system according to one or several of the preceding claims, characterized in that it comprises a bag-shaped active ingredient reservoir, comprising a liquid, highly viscous, semi-solid or thixotropic matrix.

15. Transdermal therapeutic system according to claim 14, characterized in that the bag-shaped active ingredient reservoir comprises a gellant.

16. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the concentration of the acetylsalicylic acid and/or salicylic acid ranges between 5–75%, preferably between 15–45% with respect to the total mass of the active ingredient-containing layers.

17. Method for the manufacture of a transdermal therapeutic system according to one or more of the preceding claims, characterized in that the pyrrole derivatives and terpene components are coated onto an active ingredient-containing matrix layer as mixture or solution individually or after one another.

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(57) Abstract: The invention relates to a transdermal, therapeutic system in the form of a plaster which contains acetylsalicylic acid and/or salicylic acid. Said system has a backing layer, an active ingredient reservoir attached thereto, a membrane which controls the administration of the active ingredient in the absence of other control mechanisms, an adhesive device for fixing the system onto the skin and a protective layer which can be detached before application. The system is characterised in that it contains at least one component from the group of pyrrol derivatives and at least one component from the group of terpenes.

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 197 01 059 A (LTS LOHMANN THERAPIE-SYSTEME GMBH) 16 July 1998 (1998-07-16) the whole document	1-17
Y	EP 0 356 382 A (CIBA-GEIGY AG) 28 February 1990 (1990-02-28) the whole document	1-17
A	GB 2 141 025 A (NITTO ELECTRIC INDUSTRIAL CO LTD (JAPAN)) 12 December 1984 (1984-12-12) page 6; example 16	2

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	DE 43 32 093 A (LTS LOHMANN THERAPIE-SYSTEME GMBH & CO KG) 23 March 1995 (1995-03-23) column 1, line 1 - line 8 column 4, line 23 - line 46	1-17

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